INFLUENCE OF GEOMETRICAL NUCLEAR PROPERTIES ON CHROMOSOME ABERRATION

Floriane Poignant [1,*], Ianik Plante [2], Janice L. Huff [3], Tony C. Slaba [3]

[1]National Institute of Aerospace, Hampton, VA 23666, [2]KBR, 2400 NASA Parkway, Houston, TX 77058, [3]NASA Langley Research Center, Hampton, VA 23681. * **Correspondence**: floriane.a.poignant@nasa.gov

Background

- **Space radiation.** Among main hazards for space flight, primarily due to galactic cosmic ray high charge and energy (HZE) ions.
- **Relative biological effectiveness** (RBE). Important factor used to estimate space-radiation quality factor in cancer risk models [1].
- **Chromosome aberrations** (CA). Possible biomarker to assess HZE ion RBE and related cancer risks [2].
- Role of nuclear **3-dimensional (3D) genomic organization** on the formation of CAs remains to be understood [3].

Objectives

- To assess how **change in nuclear properties and chromosome organization impacts CA formation in terms of RBE values.**
- To **compare to experimental results** for heavy ions of linear energy transfer (LET) relevant to space radiation [4-7].

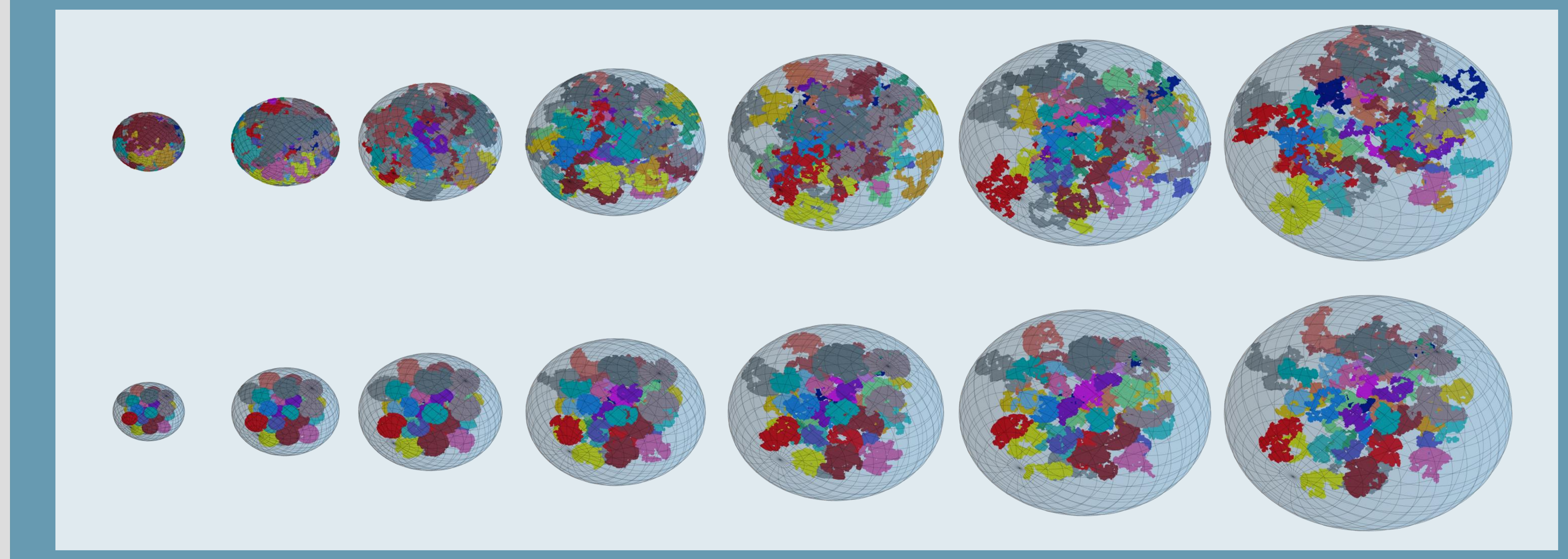
Material & Methods

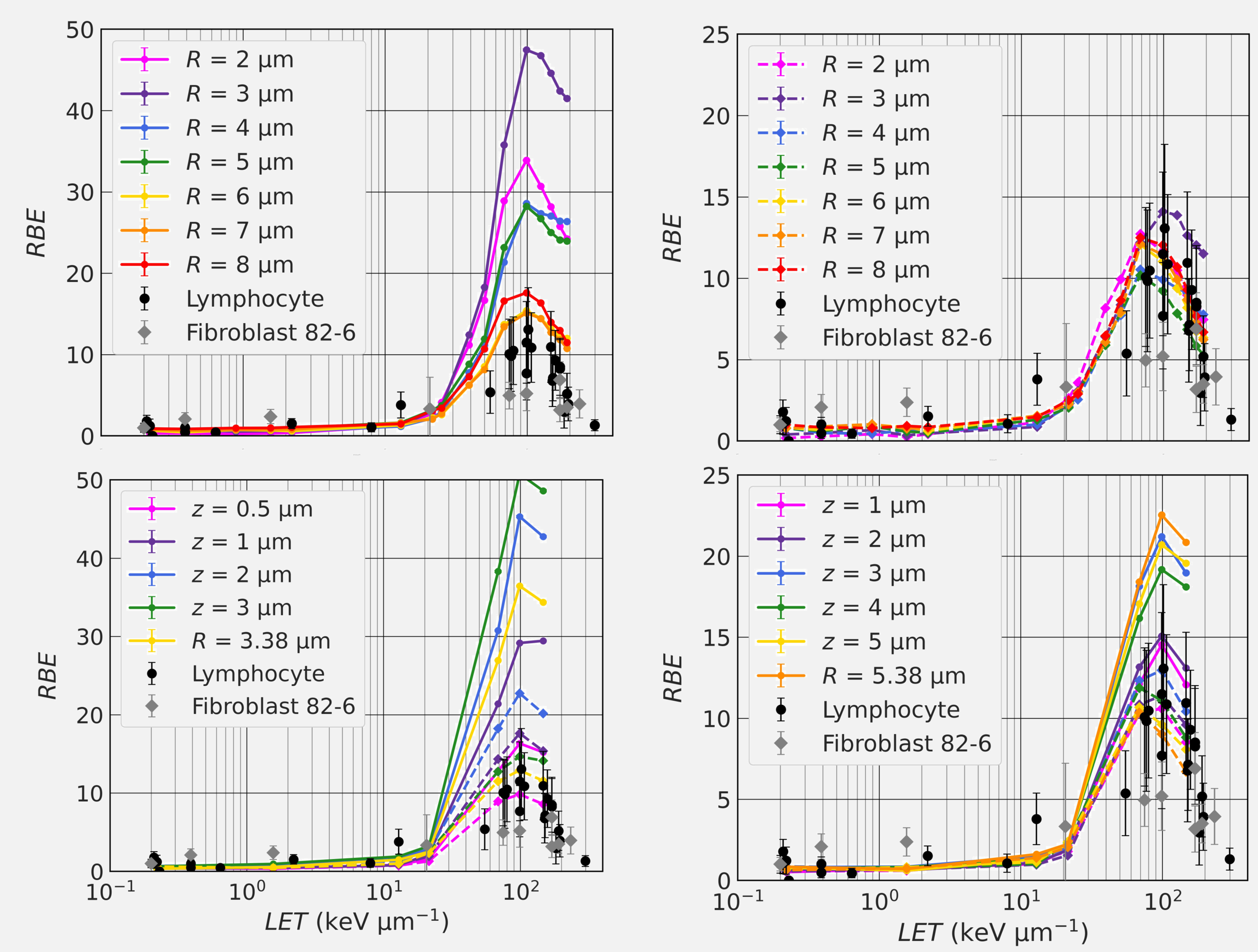
- 46 interphase chromosomes modelled as monomer sequences distributed in the nucleus with a random walk. Chromosomes associated with non-overlapping domains.
- Two chromosome **intermingling configurations**:
  - **Min.** Monomer sequence constrained in domains.
  - **Max.** Only first monomer of sequence constrained in domains.
- Cell **nuclei geometries**
  - Spherical with radii R varying from 2 µm to 8 µm.
  - Ellipsoidal with volume $V = 162$ µm³ (fibroblast AG1522) or $V = 656$ µm³ (fibroblast 82-6) and thicknesses z varying from 0.5 µm to 5.38 µm.
- Monte-Carlo **track-structure** tool **RITRACKS** [8] used for **transport** of **HZE ions and γ-rays** (0.6617 MeV) in cell nuclei, for doses D in the range 0 to 1 Gy.
- Monte-Carlo tool **RITCARD** [9,10] used to model DNA double-strand breaks (**DSB**) (~35 DSB/Gy/cell), DSB **(mis)-repair** for a 24h time-period and **chromosome aberration classification**.
- Linear quadratic dose response for **total exchange**

$$\boldsymbol{y(D) = \alpha\, D + \beta D^2} \text{ and } \boldsymbol{RBE = \alpha_{\mathrm{HZE}}/\alpha_\gamma}$$

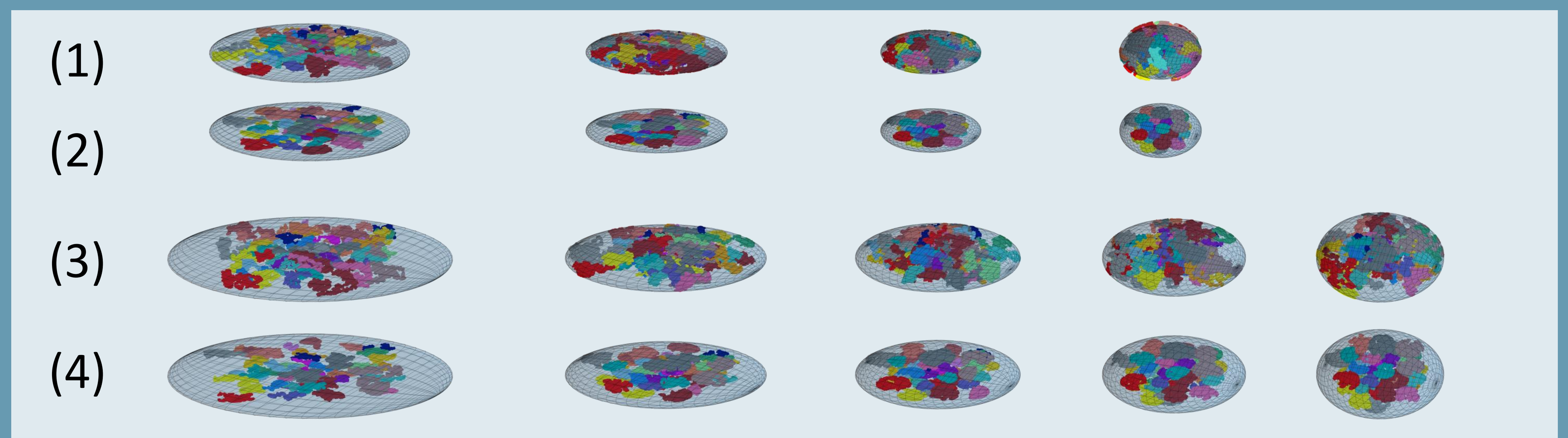
Results & Discussion

Chromosome distribution in spherical nuclei with radii increasing from 2 µm to 8 µm. Top: maximum intermingling. Bottom: minimum intermingling.





RBE as a function of LET for total exchanges. Exp. data from [4-7]. Top Spherical. Bottom: Ellipsoidal; left: AG1522 ($V = 162$ µm³), right: 82-6 ($V = 656$ µm³). Solid: max. intermingling. Dashed: min. intermingling.



Chromosome distribution in ellipsoidal nuclei. (1) & (2) $V = 162$ µm³, $z \in$ 0.5 µm to 3 µm. (3) & (4) $V = 656$ µm³, $z \in$ 1 µm to 5.38 µm. (1) & (3) Maximum intermingling. (2) & (4): minimum intermingling.

- **LET effect**
  - RBE peaks at ~ 100 keV/µm regardless of size, shape or chromosome intermingling, consistent with experimental data.
  - Little dependence on 3D genomic organization for low-LET ions.
- **Size effect**
  - RBE dependence on R for high-LET ions and max. intermingling, with increase of RBE from 2 µm to 3 µm, followed by a decrease of RBE from 3 µm to 6 µm and saturation beyond.
  - Little RBE dependence on R for min. intermingling.
- **Shape effect**
  - AG1522 (small nucleus). RBE dependence on z, with increase of RBE from $z = 0.5$ µm to 3 µm and decrease for spherical nucleus for max. intermingling. Weaker dependence on z for min. intermingling, with RBE peaking for $z = 2$ µm .
  - 82-6 (large nucleus). RBE dependence on z to a lesser extent compared to AG1522. Increase and saturation of RBE with increasing z for max. intermingling. Little dependence on z for min. intermingling.
- **Min. vs. Max. Intermingling**
  - Decrease of RBE values when intermingling reduced.
  - Decrease of RBE dependence on nuclear geometry when intermingling reduced.
- **Lymphocyte vs. Fibroblast**
  - Lymphocyte. Spherical, $R \sim 3$ µm, V ~ 113 µm³.
  - 82-6. Ellipsoidal, $x = y \sim 7.22$ µm, z ~ 3 µm, $V = 656$ µm³.
  - Higher RBE values for lymphocyte vs. fibroblast, consistent with geometrical effect.
  - Comparable RBE values between experimental data and simulated results for min. intermingling.

Conclusions

- **RBE dependence on size and shape** of the nucleus, with effects **more pronounced with max. intermingling**.
- Trends due to **dependence of $\boldsymbol{\alpha_{HZE}}$ and $\boldsymbol{\alpha_\gamma}$ on 3D genomic organization** for both simple and complex exchanges [11].
- Nuclear geometrical properties to be assessed when comparing CA between cell lines of different size and shape, or when translating *in vitro* results to *in vivo* risks.

References

[1] Simonsen et al. (2021) *Life Sci. Space Res*. 31, 14-28. [2] Sridharan et al. (2016) Life Sci. Space Res. 9, 19-47. [3] McCord et al., *In Chromosome Translocation; Springer: Singapore.* **2018**, pp. 113–133. [4] George et al. Rad. Res. (2003) 160.4, 425-435. [5] George et al. (2013) Rad. Res. 180, 25–33. [6] Hada et al. (2014) Rad. Res. 182, 368–379. [7] George et al. (2015) Front. Oncol. 5, 226. [8] Plante *et al*. *InTechOpen: London, UK.* **2011**, 315–356. [9] Plante *et al*. *Radiat. Res*. **2019**, 192, 282–298. [10] Plante *et al*. *Genes.* **2019**, 10, 936. [11] Poignant *et al*. *Int. J. Mol. Sci*. **2022**, 23, 8638. ***Use the QR code to check out our paper!***

Acknowledgement

This work is supported by NASA Human Health and Performance (HHPC) contract number NNJ15HK11B (IP) and by the NASA Langley Cooperative Agreement 80LARC17C0004 (FP). This work is supported by the Human Research Program under the Human Exploration and Operations Mission Directorate at NASA (TS, JH).

National Institute of Aerospace